CSHP Clinical Symposium - September 24, 2008

It's just not that into you:

The no-excuses truth to understanding rejection and transplant pharmacology

Erica D. Greanya, PharmD

Clinical Pharmacy Specialist
Solid Organ Transplantation

Disclosure

- I have no real or perceived conflicts of interest to declare.

Objectives

- Develop a basic understanding of the immune system and specific targets of pharmacotherapy
- Understand the rationale for specific transplant immunosuppressive regimens
  - Therapeutic effects
  - Non-immune toxicities
    - Post-transplant diabetes mellitus, cardiovascular disease
  - Effects of immune deficiency
    - Malignancy, infection

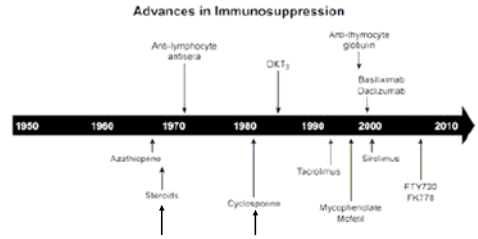
1st successful kidney transplant

- Dec 23, 1954
  - Peter Bent Brigham Hospital, Boston MA
  - Dr. Joseph Murray
- 23 yr old identical twin brothers
  - No immunosuppression used
  - d. 1962 due to disease recurrence (glomerulonephritis)

N Engl J Med 2004;351:2761-6.

N Engl J Med 2004;351:2678-80.

History of Immunosuppression in Transplantation



1 year kidney graft survival 40-50% 70-85%

Liver Transplantation 2005;11:1307-14.

Present state of transplantation

- In 2005 ~ 160,000 people in the US were living with a functioning organ transplant
  - 1-year graft survival 80-95% (all organs)
- Kidney graft t1/2 ~ 8 years
- Liver – 5 year graft survival 80%

Transplantation 2005;80:S142-6.

Drugs 2007;67:1167-98.
Am J Transplant 2004;4:378-83.

Goals of immunosuppression (IMS) in solid organ transplant (SOT)

- To prevent allograft rejection
- To prolong allograft functional life
- To optimise allograft function

- Prolong patient survival
- Improve patient quality of life
- To minimize toxicity of IMS agents
  - immunodeficiency complications
  - non-immune toxicities

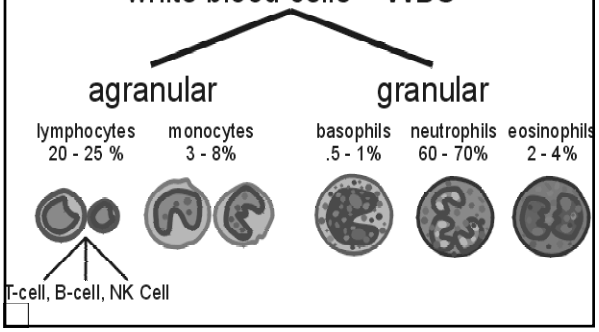
Transplantation and the immune system

- Recognition of allograft as non-self
- Donor and recipient antigen presenting cells (APC's = dendritic cells, macrophages)
  - Present donor antigen to host T-lymphocyte

Key event = T-lymphocyte activation

Leukocytes

white blood cells ~ WBC

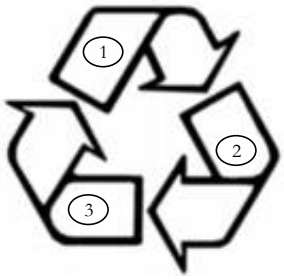


Immunosuppression: 3 ways to achieve

- Depletion of lymphocytes
  - Polyclonal antibodies (horse, rabbit anti-thymocyte globulin)
  - Mouse monoclonal anti-CD3 antibody (OKT3)
  - Humanized monoclonal anti-CD52 (alemtuzumab)
  - B-lymphocyte monoclonal anti-CD20 (rituximab)
- Diversion of lymphocyte traffic
- Blocking of lymphocyte response

NEJM 2004;351:2715-29.

Immune system: 3 signal model of T-cell activation



Signal 1: Antigen-specific signal

- Donor antigen is presented on APC (antigen presenting cell)
- T-cell recognized antigen as "non-self"
- Complex formed between MHC-Antigen-T-cell receptor (TCR)
- Immune signal is transduced through CD3 complex

N Engl J Med 2004;351:2715-29. 4th ed. Handbook of Kidney Transplantation

Signal 2: non-antigen-specific co-stimulatory signal

- Binding of co-receptors between APC and T-cell
  - CD80/86 (aka B7) on APC with CD28 on T-cell
- "reinforces" and strengthens immune signal transduced through CD3 complex
- Combined action of signals 1 & 2 activate important intracellular pathways

N Engl J Med 2004;351:2715-29. 4th ed. Handbook of Kidney Transplantation

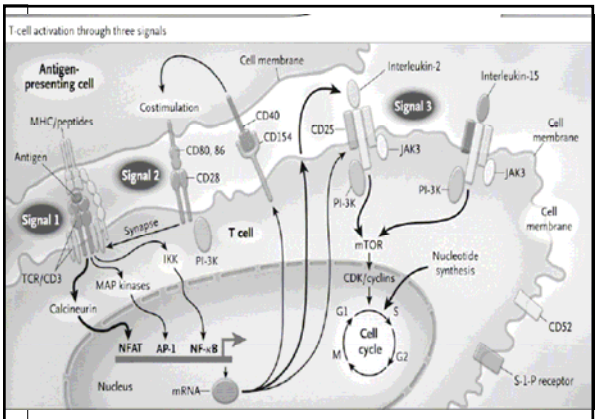
- Combined action of signals 1 & 2 activate important intracellular pathways
  - Calcium-calcineurin pathway
  - RAS-MAP kinase pathway
  - Nulcear factor-κB pathway
- Leads to
  - production of IL-2 and other growth promoting cytokines
  - expression of IL-2 receptor (CD25)

N Engl J Med 2004;351:2715-29. 4th ed. Handbook of Kidney Transplantation

Signal 3: mammalian target of rapamycin (mTOR) activation

- IL-2 produced binds to newly activated IL-2 receptor (CD25)
- Binding activates mTOR
- mTOR activation triggers cell cycle
  - Lymphocyte proliferation
  - Results in large numbers of effector T-cells

N Engl J Med 2004;351:2715-29. 4th ed. Handbook of Kidney Transplantation



N Engl J Med 2004;351:2715-29.

Result of effector T-cells

- Effector T-cells targeted at donor antigen infiltrate graft
  - Interstitial and/or perivascular infiltration
  - Cascade of activation of macrophages, B-cells, plasma cells
  - Resultant cell lysis
  - Severe – edema, hemorrhage, vasculitis

Expert Opin Pharmacother 2006;7:1139-49. N Engl J Med 2004;351:2715-29.

Immunosuppression: 3 ways to achieve

- Depletion of lymphocytes
- Diversion of lymphocyte traffic
- Blocking of lymphocyte response
  - Non-depleting monoclonal antibody
    - IL-2 receptor antagonists (basiliximab, daclizumab)
  - Calcineurin inhibitors (tacrolimus, cyclosporine)
  - Anti-proliferative agents (azathioprine, mycophenolic acid)
  - mTOR inhibitor (sirolimus, everolimus)

NEJM 2004;351:2715-29.

Effects of immunosuppression:

- Therapeutic effects
  - Prevention of rejection
- Non-immune toxicities
- Undesired consequences of immune deficiency
  - Infection
  - malignancy

NEJM 2004;351:2715-29.

CNI's: Tacrolimus and Cyclosporine

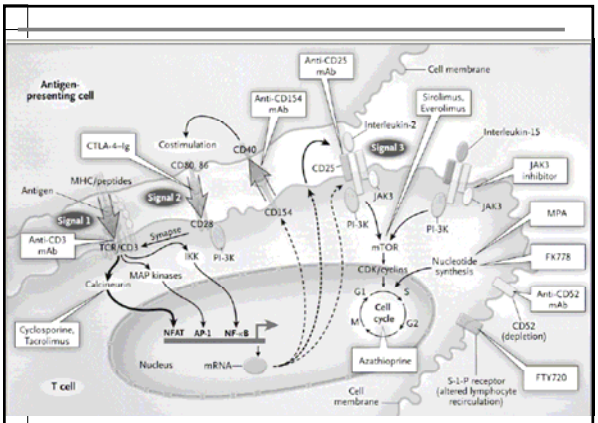
- Major breakthrough in modern transplantation
  - Lead to significant improvements in outcome
- "Backbone" of most IMS protocols
- Similar mechanisms of action
  - Differ in structure and receptor interactions

Transplant Proc 2004;36:25S-32S. Am J Kidney Dis 2006;47:S3-21.

CNI: Mechanism of action

- Forms complex with cytosolic proteins (aka immunophilins)
  - CSA = cyclophilin
  - Tacrolimus = FKBP-12 (FK-binding protein)
- ↑ affinity and binding of immunophilin-drug complex to calcineurin
- Inhibits of transcription of IL-2, other cytokines
- ↓ T-cell activation & proliferation

Transplant Proc 2004;36:25S-32S. Circulation 2004;110:3858-65.



Differences in efficacy - Kidney

- Single trials – **favors tacrolimus**
  - ↓ acute rejection episodes (AR) @ 1 yr
  - ↑ GFR @ 1 yr
  - No difference patient or graft survival to 5 yr
- Meta-analysis – **favors tacrolimus**
  - ↓ graft loss at 6 mo (RRR 44%) & 3 yr (RRR 29%)
  - ↓ AR
  - ↓ SCr and 1 year graft dysfunction

Expert Opin Pharmacother 2008;9:635-43. Cochrane DSR 2005;4.
N Engl J Med 2007;357:2562-75.

Differences in efficacy - Liver

- Cochrane meta-analysis (16 trials; n=3813)
  - Majority vs. microemulsion CSA
- Favors tacrolimus
  - ↓ mortality @ 1 yr (RR 0.85, 95% CI 0.73-0.99)
  - ↑ graft survival (RR 0.78, 95% CI 0.68-0.89)
  - ↓ AR
  - ↓ steroid resistant AR

Cochrane DSR 2006;4.

Monitoring: CNI Levels

- Concentration-based rather than dose-based
  - Narrow therapeutic window
  - Wide inter- and intra-patient variability
    - Genetic differences in CYP 3A family
    - Intestinal efflux via P-glycoprotein
- Therapeutic ranges identified which correlate well with efficacy and toxicity
  - Assay differences ~25% variation based on level of metabolites measured
- Total drug exposure found to correlate best with efficacy

Pharmacol & Therapeutics 2006;112:184-98.

Cyclosporine levels: C2 vs. C0

- Studies suggest C2 may be better than C0 for acute rejection and nephrotoxicity
  - Kidney > liver transplantation
  - Poor methodology, clinically small differences
  - Improved correlation to AUC
  - ↓ intra-individual variation
- Patient convenience
- Algorithm for both available
- Bottom line: may see C2 for kidney transplantation

Pharmacol & Therapeutics 2006;112:184-98. Ther Drug Monit 2006;28:637-42.

Tacrolimus levels

- Trough levels correlate well with AUC
  - Wide range of correlation in studies (r^2 = <0.5 – 0.85)
  - Study differences in sample size, time post-tx.
- AUC estimations available for specific patients
  - Signs of over-exposure (infection, nephrotoxicity)

Pharmacol & Therapeutics 2006;112:184-98. Kidney Int 2005;67:2440-7.

Drug interactions

- CYP-3A4 substrates
  - Azoles, macrolides, non-DHP CCB's, amiodarone
  - Rifampin, phenytoin, CBZ
- CYP-3A4 inhibitor (CSA >>> tac)
  - Statins
- P-glycoprotein

Expert Opin Pharmacother 2008;9:635-43. Transplant Proc 2004;36:25S-32S.

Management of drug interactions – no feasible alternative available:

- Consider empiric dosage adjustment if:
  - Acute renal dysfunction present
  - Average levels run in mid-high therapeutic range
  - Prolonged duration of therapy
- Empiric dosage adjustment likely not necessary if:
  - Stable, adequate renal function
  - Average levels in low-therapeutic range
  - Shorter durations of therapy
- Follow levels and adjust as needed

Monitoring parameters:

- Levels if able (target per transplant center)
- SCr
- Other symptoms of dose related CNI toxicity

Communication

- Ensure transplant center aware of admission and dosage adjustments
- Ensure patient aware of dose adjustments and follow-up required

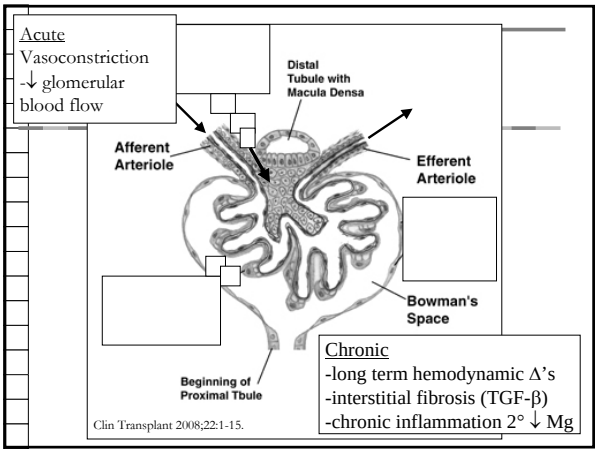
Adverse effects – Dose-related

System	CSA	Tacrolimus
CNS		Tremor, h/a, insomnia, confusion, parasthesias, dysarthria
GI	Hepatotoxicity (cholestatic)	Diarrhea
GU	Nephrotoxicity	Nephrotoxicity
	Hyperkalemia, hypomagnesemia	

CNI nephrotoxicity

- 5-7% incidence of acute renal failure
  - Dose related
  - Generally reversible
- ~50% late kidney graft loss due to CNI toxicity
- 7-21% of non-renal SOT recipients have chronic renal dysfunction @ 5 years
  - Organ dependant (liver > lung > heart)
  - ~1/3 of these will require dialysis/renal transplant
  - Associated with ↓ survival

Expert Opin Pharmacother 2008;9:635-43. Clin Transplant 2008;22:1-15



Clin Transplant 2008;22:1-15.

CNI nephrotoxicity Pharmacodynamic drug ix

- Additive nephrotoxicity
  - NSAIDS – afferent vasoconstriction
  - ACE-I/ARB – efferent vasodilation
  - Aminoglycosides, amphotericin B
- Renal sparing
  - CCB's – afferent vasodilation

Can J Cardiol 2003;16:620-54.

Adverse effects – Non-dose-related

System	CSA	Tacrolimus
CVS	Hypertension	
Metabolic	Hyperlipidemia (TC, TG) Hyperuricemia	Impaired glucose tolerance
Derm	Hirsutism Acne Gingival hyperplasia	Alopecia
Heme	Leukopenia, hemolytic anemia	

Post-transplant diabetes mellitus (PTDM)

- Registry data: ~20% @ 1yr post-transplant
- Contribute to
  - ↑ CV risk, ↑ infection
  - ↓ long term graft survival, ↓ quality/quantity of life
- Conflicting literature on CSA vs tac
  - Definitions not standard
  - Most data from era of high corticosteroid use, higher CNI levels

Expert Opin Pharmacother 2008;9:635-43. Am J Transplant 2004;4:583-95.
Nephrol Dial Transplant 2008;23:1816-18.

Post-transplant diabetes mellitus (PTDM)

- Meta-analysis
  - Renal: RR 1.86 – 3.86 with tacrolimus treatment
  - All organs: Tacrolimus 16.6% vs. CSA 9.8%
  - ↑ risk with ↑ tacrolimus trough levels
- Mechanism
  - Dose dependant ↓ insulin secretion via direct β-cell toxicity or DNA inhibition
  - Insulin resistance
  - Inhibition of steroid metabolism
  - More FKBP in pancreatic β-cells?

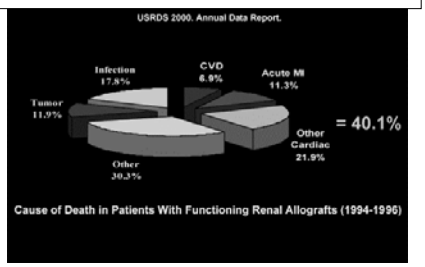
Cochrane DSR 2005;4.
Am J Transplant 2007;7:1506-14.
N Engl J Med 2007;357:2562-75.
Am J Transplant 2004;4:583-95.

Global cardiovascular risk

- ↑ in short term graft function have shifted focus to long term ↓ mortality
- ↑ rates of CV mortality in SOT population
  - Pre-existing disease
  - Effects of immunosuppressants
  - Note: high risk patients would be excluded from transplantation in the first place!!

Transplantation 2007;83:1141-50.
J Hypertens 2005;23:1609-16.

Burden of cardiovascular disease



Aggressive risk factor management

- Hypertension
- Hypercholesterolemia
- Diabetes mellitus
- ASA 1° prevention
  - Framingham score has been validated in renal tx although underestimated risk, especially in DM
- Immunosuppression modification
  - Conversion from CSA to tac (↓ CV risk in renal tx)
  - Steroid minimization protocols

Lancet 2002;359:741-6.
Transplantation 2007;83:1141-50.
Am J Transplant 2003;3:982-7.
J Hypertens 2005;23:1609-16.

Bottom Line: CNI's

- Backbone of regimens: ↓↓ AR rates and improved short term outcomes
  - Non-immune toxicities may contribute to impaired long-term outcomes (↑ CV risk, nephrotoxicity)
- Tacrolimus has become CNI of choice
  - Improved efficacy - ↓ rejection rates & graft loss
  - Less nephrotoxicity
  - Less drug interactions – minimal 3A4 inhibition
  - Greater incidence of PTDM and neurologic complications

Anti-metabolites/Antiproliferatives

- Azathioprine - Imidazole prodrug
  - Rapid conversion to 6-mercaptopurine (6-MP)
  - 6-MP→thio-inosine-monophosphate→purine analog
- Mycophenolate Mofetil - mycophenolic acid (MPA) prodrug
  - Reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH)
  - Rate limiting enzyme in *de novo* purine synthesis

Mechanism of action

- Azathioprine - incorporated into DNA as "false" purine; enzyme inhibition of DNA precursors
- MPA – inhibits purine synthesis
- Inhibits synthesis and proliferation of T & B-lymphocytes
  - Inhibits antibody formation
  - Inhibits generation of cytotoxic T-cells

Circulation 2004;110:3858-65. Liver Transplant 2005;11:1307-14.

MMF other effects

- Inhibits recruitment of mononuclear cells into rejection sites
  - May have role in tx of ongoing rejection
- Minimal effect on cytokine production
- ↑ lymphocyte selectivity vs. azathioprine
  - Lymphocytes lack alternate "salvage" purine synthesis pathways
  - ↓ myelotoxic and hepatotoxic adverse effects vs. AZA

Circulation 2004;110:3858-65. J Hepatol 2003;39:664-78.

Differences in efficacy - Kidney

- 3 main large mulitcenter RCT's
  - All CSA + prednisone
  - MMF 1g BID vs. MMF 1.5g BID vs. AZA/placebo
- Significant ↓ AR @ 6-months with MMF
- Pooled analysis
  - AR @ 1 yr 19.8% vs. 16.5% vs. 40.8%
  - No difference graft failure or patient survival to 3 yrs
    - Graft failure @ 3 yrs OR 0.72 for MMF 2g/d (p = 0.05)

Transplantation 2005;80:S191-200. Transplantation 1997;63:39-47.

Differences in efficacy - Kidney

- With tacrolimus
  - ↓ AR @ 1 yr with MMF 1g BID vs. AZA
  - No difference graft or patient survival
- USRDS registry data vs. AZA
  - Significant ↑ graft and patient survival at 4 years
  - Patient survival 91.4% vs. 89.9% (p = 0.002)
  - Graft survival 85.6% vs. 81.9% (p<0.0001)

Transplantation 2000;69:2405-9 Transplantation 2000;69:875-80.

Differences in efficacy - Liver

- RCT MMF vs. Azathioprine with CSA+pred (n = 565)
  - AR or graft loss @ 6 mo 38.5% vs. 47.7% (p<0.03)
  - AR @ 1 yr 31% vs. 40%
  - No difference graft or patient survival @ 1 yr
- Registry and small trial data on MMF
  - ↓ late AR vs. placebo
  - Improved 4 yr patient and graft survival vs. placebo
  - Improved CNI and steroid sparing abilities

Liver Transpl 2001;7:442-50. J Hepatol 2003;39:664-78.
Transplantation 2005;80:S142-6.

Adverse Effects

Azathioprine

- Hematologic
  - Neutropenia
  - Anemia
  - Thrombocytopenia
- GI
  - Hepatitis, cholestasis
  - Pancreatitis

MMF

- Hematologic
  - ↓ vs. azathioprine
- GI
  - Diarrhea
  - Heartburn/gastritis
  - Abdo pain
- Infections
  - Viral (CMV, HSV)
    - ↑ with ↑ doses

Bottom line: anti-metabolites

- MMF
  - ↓ short term AR and possible ↑ graft and patient survival
- Kidney transplantation
  - MMF 1g po BID has replaced Azathioprine
  - ↓ efficacy with 500mg BID; ↑ CMV infection with 1.5g BID
- Liver transplantation – less data available
  - Effective in targeted populations
    - Chronic renal dysfunction - allows ↓ CNI without ↑ AR
    - Replace azathioprine in recurrent/severe rejection
    - Steroid sparing

Transplantation 2005;80:S191-200.

The downside to MMF

- ↑ symptomatic GI toxicity
  - H2-blocker or proton pump inhibitor
  - Dose reductions (compramised efficacy?)
  - Alternative dosage forms: enteric coated mycophenolate sodium
- Cost

The cost of maintenance therapy

Drug	Dose	Target	Cost/month (ave. dose)	Cost per drug level
CSA Tacrolimus	3mg/kg bid 0.075mg/kg bid	T-cell	$750	$26.73
Sirolimus	2-5 mg/d	T-cell >> B-cell	$420 - 1000	$ ~30
Azathioprine MMF	1-2mg/kg/d 2-3g/d	T/B-cells	$10 $500 - 750	N/A $53.19
Cortico-steroids	5-20 mg/d	T/B-cells	$1 - 5	N/A

Current IMS protocols

- Tacrolimus backbone
- Anti-metabolite
- ± corticosteroids

Goals of IMS

- prevent allograft rejection
- prolong allograft life
- optimise allograft function

- Prolong patient survival
- Improve patient QoL
- To minimize toxicity of IMS agents
  - immunodeficiency complications
  - non-immune toxicities

The downside to current IMS

- Graft t1/2 has remained essentially unchanged
  - Chronic rejection
  - Renal graft toxicity – CNI nephrotoxicity
  - Infectious graft/patient loss
  - Death with functioning graft
    - Cardiovascular disease
    - Malignancy

Account for ~50% of graft losses

Nephrol Dial Transplant 2007;22:viii61-5. Clin Transplant 2006;20:30-43.

Mammalian target of rapamycin (mTOR) inhibitors

- Sirolimus (Rapamycin) - 2001
  - Macrolide antibiotic (structure similar to tacrolimus)
  - First isolated in soil samples from which island?

Mechanism of action: Proliferation signal inhibitor

- Complex formation with FKBP-12 (same as tacrolimus)
- Complex binds mTOR regulatory kinase
  - vs. calcineurin phosphatase like tacrolimus
  - Signal 3
- Arrest of cell cycle (G_1 – S phase)
- ↓ T & B-cell proliferation

Drugs 2007;67:369-91. NEJM 2004;351:2715-29.

Extended mechanisms…. mTOR is everywhere!

- Non-immune proliferation inhibition
  - Vascular smooth muscle cells
    - ? Anti-atherogenic
  - Endothelial cells
  - Fibroblasts (important in wound and tissue healing)
  - Hematopoietic cell lines
  - Malignant cell lines
    - Lymphoid, CNS, hepatic, melanocytic, renal

Clin Transplant 2006;20:30-43. Drugs 2007;67:369-91.

Adverse effects

- Dose-related
  - Hyperlipidemia (↑TG, LDL, HDL)
  - Anemia, leukopenia, thrombocytopenia
  - Peripheral edema, pleural/pericardial effusions
  - Painful mouth ulcers
- Non-dose-related
  - Impaired wound healing
    - post-op fluid collections and anastomotic complications
  - Acne, skin rashes
  - Pulmonary toxicity: BOOP, fibrosis, pneumonitis

Curr Opin Cardiol 2007;22:111-6. Drugs 2007;67:369-91.

Adverse effects – the upside

- Relative lack of nephrotoxicity
  - Synergistic nephrotoxicity with CNI's
  - Can ↑ proteinuria if established renal insufficiency
- Cardiovascular risk profile
  - ↑ lipids but in context of anti-atherogenic properties
  - Less PTDM
    - May still ↑ insulin resistance
  - Less HTN

Drugs 2007;67:369-91. Clin Transplant 2006;20:30-43.

Role in *de novo* transplantation

- Multiple large RCT trials conducted to determine efficacy and safety of sirolimus
  - Combination with CNI
  - Combination with anti-metabolites
  - ± corticosteroids

Role in *de novo* liver transplant

May 14, 2002 Dear Health Care Provider:

Liver Transplantation - Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT):

The use of sirolimus with tacrolimus or cyclosporine in *de novo* liver transplant recipients was associated with excess mortality and graft loss. The use of sirolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death.

The safety and efficacy of sirolimus has not been established in liver transplant patients, and therefore, such use is not recommended.

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2002/rapamune_hpc-cps-eng.php

Role in *de novo* kidney transplant

August 18, 2006 Dear Health Care Professional,

Subject: Association of a Rapamune® (sirolimus) containing immunosuppressant regimen with a high rate of acute rejection in *de novo* renal transplant

Based on information from recent clinical trials, the use of Rapamune, mycophenolate mofetil (MMF), and corticosteroids, in combination with IL-2 receptor antibody (IL2R Ab) induction, is not recommended in the *de novo* organ transplant setting.

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/rapamune_3_hpc-cps-eng.php

Role: conversion therapy

- CNI –associated side effects
  - Nephrotoxicity
  - Neurotoxicity
- MMF-associated side effects (with tacrolimus)
  - Neutropenia, diarrhea
- Refractory rejection
- Malignancy

Clin Transplant 2006;20:30-43. Drugs 2007;67:369-91.

Effects of over-immunosuppression:

- Therapeutic effects
  - Prevention of rejection
- Non-immune toxicities
- Undesired consequences of immune deficiency
  - Malignancy
  - Infection

NEJM 2004;351:2715-29.

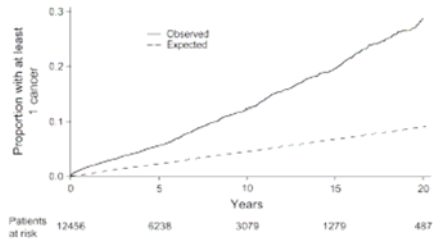
Risk of malignancy

- On average 3-5 fold higher than general population
  - Non-melanoma skin cancer & B-cell lymphoma (post-transplant lymphoproliferative disorder (PTLD)) 10-30 x higher
  - Renal cell carcinoma 15 x higher
  - Liver, bladder, vaginal, thyroid, ENT cancers 2-5 x higher
- Linked with duration and intensity of IMS
  - ↑ incidence with time post transplant

Nephrol Dial Transplant 2007;22:i36-i41. Transplantation 2005;80:S254-64.

Cumulative risk of at least 1 cancer

(not including non-melanoma skin cancers)



Transplantation 2005;80:S254-64.

Expanded risk factors in SOT

- Environmental
- Genetic
- Demographic
- Pro-oncogenic viruses
  - EBV, HBV/HCV, HPV etc.
- Immunosuppressive agents
  - ↓ immunosurveillance (lymphocytes important in controlling tumor and metastatic growth)
  - Direct carcinogenic effect

Drugs 2007;67:1167-98.

Reported data with immunosuppressants

Table 1. Impact of immunosuppressive agents on the risk of post-transplant malignancies

Immunosuppressive therapy	Organ	Observations/results
Induction therapy		
OKT3/ATG induction therapy	Heart/kidney/other	Increased risk of lymphoma
IL-2 induction therapy	Heart/kidney/other	No increased of lymphoma
OKT3/ATG	Kidney	Increased risk of lymphoma
Anti-metabolites		
Azathioprine	Kidney	Reduced risk of lymphoma
Mycophenolic acid		
MMF	Kidney	No increased risk of lymphoma or other malignancies in UNOS or CTS registries
MMF *vs* azathioprine	Kidney	Decreased risk of PTLD with MMF
MMF *vs* No MMF	Kidney	Increased risk of in Kaposi's sarcoma, possibly due to MMF
MMF	Kidney	Reduced risk of lymphoma
CNIs		
Tacrolimus *vs* new CsA formulations (no induction therapy)	Kidney	higher risk of lymphoma with tacrolimus
Tacrolimus *vs* CsA	Liver	No difference in rate of neoplastic disease
Tacrolimus *vs* CsA	Heart/kidney/other	Doubled risk of lymphoma with tacrolimus
CsA	Kidney	Three-fold increase in non-melanoma skin cancer
CsA	Kidney	Increased risk of neoplastic disease
CsA in maintenance therapy	Heart/kidney/other	No increased risk of lymphoma
Full-dose CsA *vs* low-dose CsA	Kidney	Dose-dependent increase in cancers
CNI *vs* antimetabolites		
CsA *vs* azathioprine	Kidney	Increased risk of cutaneous dysplasia with CsA
PSI *vs* CNI		
Sirolimus + CsA *vs* sirolimus and no CsA	Kidney	Increased risk of all cancer and skin cancers with CsA
Sirolimus *vs* CsA	Kidney	Increased risk of all cancers with CsA
PSI *vs* CNI	Kidney	Increased risk of all cancers and solid-organ cancers with CNI

PSI = proliferation signal inhibitor

Nephrol Dial Transplant 2007;22:i36-i41.

Sirolimus in malignancy

- Observational data from registries vs. standard triple therapy
  - ↓ *de novo* malignancy
  - ↓ lymphoma, renal cell carcinoma, skin tumors
- Effects enhanced when other agents are able to be withdrawn

Transplantation 2005;80:S254-64. Drugs 2007;67:1167-98.

Final thoughts on sirolimus

- Not first line agent
  - ↓ efficacy and wound healing concerns
- Conversion in stable patients
- Monitoring
  - Therapeutic drug monitoring (trough levels)
  - Drug interactions (CYP 3A4 substrate)
  - CV risk reduction

Effects of over-immunosuppression:

- Therapeutic effects
  - Prevention of rejection
- Non-immune toxicities
- Undesired consequences of immune deficiency
  - Malignancy
  - Infection

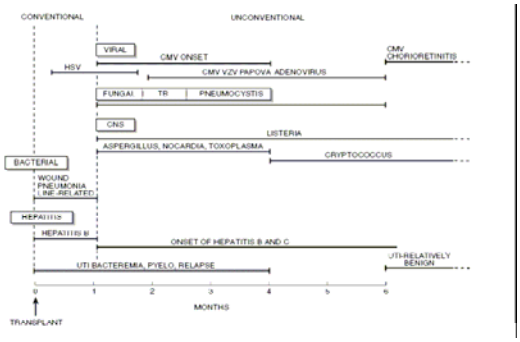
NEJM 2004;351:2715-29.

Infections in SOT recipients

- Risk of infection related to:
  - Intensity of microbial exposure
  - Net state of immunosuppression
- Consequences of infection:
  - Direct – clinical syndromes
  - Indirect – further immune suppression, allograft injury, malignancy
- Prevention has become primary goal

N Engl J Med 1998;338:1741-51. Am J Transplant 2004;4:s6-9.

Timetable of infection



Am J Transplant 2004;4:s6-9.

Ancillary therapy: Prevention of infection in SOT

- Pneumocystis jiroveci pneumonia (form. PCP)
  - Trimethoprim-sulfamethoxazole x 4-12 months
  - 10-12% → eliminated
- Cytomegalovirus (CMV)
  - Activation of latent virus
  - Prophylaxis depends on specific risk of patient
  - Ganciclovir, valganciclovir

N Engl J Med 1998;338:1741-51. Am J Transplant 2004;4:s6-9.

Approach to Pharmacotherapy in SOT patients

- Therapeutic effects
  - Prevention of rejection, knowledge of rejection history
- Non-immune toxicities
  - Close follow up of labs and patient reports
  - Aggressive treatment of CV risk factors
- Undesired consequences of immune deficiency
  - Close surveillance of malignancy
  - Prophylaxis and surveillance of infection

Questions??